THE THERAPEUTIC USE OF VITAMIN C*

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THE therapeutic use of vitamin C means to me the treatment of scurvy for I know of no important uses of the vitamin other than the prevention of what are scorbutic manifestations. The relationship between the vitamin and scurvy is extremely intimate. The presence of the vitamin in the body tissues is simply the antithesis of scurvy. The action appears to be direct and certain phenomena of scurvy have even been observed *in vitro*.

In the past, scurvy was studied when it was prevalent, but our current interest in it is not due to its prevalence but to the stimulating work of the chemists in recognizing and identifying vitamin C. This has improved our methods of studying scurvy and influenced our conception of it. All of these things may best be reviewed by a brief chronological résumé of the past twelve years. If my review is too personal a record of events in which I have played a wholly unimportant part, please forgive me. An army of workers has tramped these roads and only a few have become familiar to me. Moreover I have seen all of the developments in the light of my own experience.

Our knowledge of scurvy was considerable before vitamins were discovered. Indeed scurvy was the first deficiency disease to be recognized as such. This happened one hundred and fifty years ago. It was experimentally produced and studied thirty-two years ago and was at that time the best understood of all the deficiency diseases.

So matters stood a dozen years ago. At that time Wolbach and Howe[1] published their beautiful anatomical studies of the experimental disease and shortly afterward a large, steady supply of scorbutic guinea pigs became available to me from the biochemical laboratories of Teachers College. There, as in many another laboratory, various foods were being assayed for vitamin content by feeding experiments. In the case of vitamin C the Sherman-LaMer technique was almost universally used. This consisted of feeding young pigs graded amounts of the vitamin during a test period of three months and diagnosing the effect by a gross examination of the animals. Fragility of the jaw, painful extremities, hemorrhages

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in the muscles and the weight curve were the criteria used. It is interesting to recall that all of the important advances in the art of canning, so far as they relate to vitamin C, were gained through countless laborious experiments of this kind. Patient assistants went from cage to cage and tier to tier pipetting measured amounts of food stuffs into the mouths of reluctant guinea pigs.

Even at that time the most active searcher for the vitamin, Sylvester Soloman Zilva,[2] had observed that fresh fruit juices bleach indophenol. Only an unfortunate error, based largely on the wish to be as precise as possible, prevented him from recognizing that the reducing power of fruit juices, as measured by indophenol titrations, is due to vitamin C. However, the feeling seemed general in most laboratories that vitamin C would never be isolated because of its instability. Zilva's courage in undertaking a most unpromising line of research was widely acknowledged.

Zilva's observation of the indophenol reaction led to a chain of events which resulted in the isolation of vitamin C. In Frankfurt, Tillmans and Hirsch[3] adopted the indophenol method as a means of controlling the quality of fruit juices being sold in their city, a matter in which the civil authorities were interested. They discovered that only fresh juices gave the reaction Zilva described, not stale juice nor artificial juice. Tillmans suspected the significance of these results at once. Zilva had observed that when decitrated lemon juice was first oxidized with indophenol it remained potent, but that on standing it lost its antiscorbutic effect. He thought that the indicator was decolorized by a substance closely associated with the vitamin which tended to prevent its oxidation. Tillmans suggested the correct explanation; namely, that the oxidation was reversible and that the first stage of oxidation left the vitamin more prone to further oxidation than when in its original, reduced form.

Szent-Györgyi[4] had, the year following Zilva's study of the indophenol reaction, isolated a reducing substance from adrenal cortex and suggested its identity with the reducing substance described by Zilva in lemon juice. Within a few years the many similarities and the distribution of these substances became clear and Szent-Györgyi and associates in Cambridge and Waugh and King[5] in this country completed the chemical studies leading to our present knowledge of the vitamin. Thus occurred what we may consider to be the important contribution of our time to the story of scurvy.

During these years I was examining the tissues of guinea pigs and learning to recognize the scorbutic process. The material immediately suggested a rather interesting line of thought, for since the animals were as uniform as possible to begin with and all had been on the experimental diets for an equal number of weeks, they were naturally most suited to a study of the effect of various degrees of deficiency. This I endeavored to do and quickly discovered that I was able to recognize distinct anatomical effects of deficiencies which were never recognized clinically, even by individuals with long experience with the experimental disease. In other words, amounts of vitamin believed to be adequate for guinea pigs actually resulted in microscopic changes characteristic of scurvy. The amount of vitamin believed to be adequate for the prevention of scurvy had to be doubled to prevent certain skeletal lesions. From Sweden, Axel Höjer,[6] at about this time, called attention to the sensitivity of the lesions in the teeth and demonstrated how they might be used in improving the biological assay methods and in shortening the test period. Because few biological chemists were prepared to make histological examinations, Celia Zall and I[7] developed a method whereby the rate of growth of the incisors of the animals could be measured and the growth rate used as a criterion of the degree of protection against scurvy. This proved still more sensitive to the effects of subclinical scurvy and showed that approximately three times the accepted protective amount was necessary to give maximum growth.

All of these methods were rendered obsolete before anything further was done with them by the chemical studies already mentioned and the wide adoption of the indophenol method for assaying vitamin C sources, a method which accomplishes in several minutes what previously had required three months. But to me the experience had served as a very impressive demonstration of the wide difference between clinical freedom from scurvy and optimal vitamin C nutrition. Many others reached the same position from different roads so that the growth of this idea occurred very quickly.

Our immediate impulse was to test the theory in man, and in many postmortem examinations since then I have searched for manifestations of scurvy. It was therefore not surprising to me when several years ago Park[8] reported a surprisingly high incidence of both radiographic and anatomic evidence of scurvy in 125 children studied thoroughly with scurvy and rickets in mind. Scurvy may be found, both clinically and

anatomically, if the search be thorough—evidence, no doubt, that many of our people still live on the borderline of vitamin C deficiency. But the search went on for clinical criteria of this mild form of scurvy. The progress of these studies in the years immediately preceding the discovery of the vitamin was based on studies of the capillaries. The capillary resistance test was first tried on scorbutic guinea pigs and later applied to apparently healthy individuals. This showed that the incidence of capillary fragility was surprisingly high, approximately 30 per cent among certain groups.

The capillary test, especially as performed with a tourniquet, is of course familiar to all of you. Hess,[9] years before my own experience, had used it to advantage in studying what he called latent scurvy and more than a generation earlier rather similar observations were made by Auspitz[10] while cupping patients.

Everyone who has used the test has learned to regret its variability and inconstancy and to deprecate its diagnostic value. Hess, however, found it distinctly positive in most cases of scurvy and we believed the average value in large groups of individuals might be still more reliable. Thus we hoped to learn about the adequacy of the vitamin C intake of different economic groups. It was also evident that capillary fragility was diagnostic if a prompt response followed specific therapy. Furthermore it was generally agreed and had been the experience of many generations of medical men that the hemorrhagic diathesis was the most characteristic manifestation of scurvy. We might expect capillary changes to be the first and most delicate manifestation of scurvy, so there existed some tantalizing reasons for treating the capillary test seriously. At any rate, many studies were made with it which showed a large part of the general population to have fragile capillaries with a rough agreement between vitamin C intake and the level of the resistance. In my own laboratories these results were supported by feeding experiments in which extracts of human tissues from the postmortem room were assayed biologically and vitamin deficiency demonstrated to be common in this way.

But soon the chemical methods were introduced and displaced the capillary test. Interestingly enough, they have also shown approximately the same incidence of partial starvation of vitamin C as the capillary tests did but the proponents of one test seldom find individual agreement between the two techniques.

The weakness of the chemical method has been that it does not of

TABLE I

CHEMICAL AND CLINICAL TESTS FOR SCURVY

	Fasting Blood (Mgs. per cent)	*Capillary Resistance. (Cm.Hg. neg. pressure)*	*Urinary Excretion following a test dose (Mgs.)*
Normals	0.80	45	44.0
Subclinical Scurvy	0.36	29	24.0
Severe Scurvy	0.064	5	2.0
Peptic Ulcer with Hemorrhage	0.33	11	8.0
Nonscorbutic Hemorrhagic Diseases	1.27	22	58.0

(With the exception of the case of severe scurvy the values are given as the averages for small groups of patients.)

itself demonstrate at what level of saturation or blood concentration of vitamin, deleterious effects occur. There have, it is true, been a few observations of associated gingivitis, but little of much weight. Most of these studies have been made by biological chemists with poor facilities for clinical observation.

Sloan and I[11] studied cases of manifest scurvy, mild or doubtful scurvy and normal individuals by all of the suggested methods including the capillary test. It was found that the fasting blood level, of all the single, simple procedures, furnishes the best evidence of vitamin C nutrition. Only the blood curve following a test dose is more precise. The total urinary excretion during twenty-four hours is frequently misleading although the excretion curve during the six hours following a test dose and even the total excreted vitamin during that period are fairly reliable. It was also found that the capillary test was as a rule positive in those individuals showing partial saturation. I have summarized the results from what we considered the best tests in Table I.

In general they conform with the experience of others. Several things may be learned from them. The fasting blood level clearly mirrors the condition of these individuals and nicely distinguishes between the frank scorbutic, the subclinical scorbutic and the normal. The capillary resistance test does likewise but is misleading in two groups. In the cases with ulcer, two-thirds of the patients gave false negative results, presumably because they were so exsanguinated that their superficial vessels were empty of blood, and rupture, if it did occur, could not be recognized.

The nonscorbutic group of hemorrhagic diseases, including a case of thrombocytopenic purpura, gave false positive results. In the first group, once relief was afforded the anemia, more revealing capillary tests were secured and these improved under vitamin treatment. In the second group no change followed treatment.

The table seems to me to serve two purposes. In the first place, the definite association of capillary fragility with degrees of unsaturation believed to be abnormal, constitutes definite objective evidence that the condition of subclinical scurvy has at least one morbid manifestation. This can be correlated with the observations already mentioned to constitute a continuous chain of evidence indicating that such degrees of deficiency are actually degrees of scurvy and not within the normal range. But much more will be required to be certain of this most fundamental point. The second use of the table is that it illustrates the methods by which vitamin C absorption, storage and excretion may be studied.

Nutrition is properly a major concern of our public health services. But there is a field of pathological deficiency in nutrition which is wholly within the practice of clinical medicine. Thus you may recall in the first of my tables the low blood concentration of vitamin C and the low urinary excretion of a small group of cases of peptic ulcer complicated by massive hemorrhages. Table II contains other information on one of these patients. You will note that, coincidental with saturation, the bleeding stopped. We have seen various cases of this kind and most of these proved to be deficient in vitamin C. This is representative of the applications we can make of our newly acquired knowledge.

There are various other similar conditions. Almost all of these seem related to known facts concerning scurvy. For example, the healing of surgical wounds may be hindered by vitamin C depletion. There is no doubt that this does occur experimentally. The issue at present is solely whether a sufficient degree of deficiency occurs in our surgical clinics to prevent union. Several writers have found cases which suggest this. The product of fibroblasts, collagen, does not form in the absence of vitamin C either *in vivo* or *in vitro*. Therefore any condition in which defective scar tissue occurs might well be held suspect, just as idiopathic hemorrhage should suggest scurvy. The laboratory can supply evidence of value, as I have shown, and the therapeutic test is usually conclusive.

Various such peculiar manifestations of scurvy are secondary in nature. Thus the ulcer patient may be presumed to have faulty absorption

TABLE II

USE OF VITAMIN C IN A CASE OF PEPTIC ULCER WITH HEMORRHAGE

Day	*Urinary Output in Vitamin C		Vitamin C Intake (mgs.)	Blood vitamin (mgs. %)	Blood in stool	Blood	
	in 6 hrs. (mgs.)	in 24 hrs. (mgs.)				Hg b. (%)	RBC (mil.)
1					4+	32	0.97
2						33	2.4
5					4+	52	
13					4+	53	3.0
22	18 (4%)	11	1000				
23	30 (6%)	54	500				
24	52 (10%)	65	500		1+		
25	134 (27%)	125	500	0.50		65	3.8
26	210 (40%)	156	500				
27	201 (40%)	202	500				
28	238 (48%)	225	500	1.05	2+	69	4.0
31-35			oral		—		
75	698 (70%)	702	1000	1.10	—		
92			oral	0.95	—		
115			oral	1.07	—		

(The lower values of excreted vitamin C in the twenty-four hour period represent losses incidental to storage overnight.)

although some are probably depleted by too restricted diets. The presence of a serious disease in no way minimizes the requirement, the insistent requirement, for the vitamins. Thus infectious diseases increase the requirements. Factors such as activity and physical exertion are important. This is by no means a new observation. The old sailing captains complained that their best, most energetic seamen were the first to be incapacitated by the scurvy, the loafers suffered last.

These are but a few of the possibilities which must be explored in explaining the unexpected cases of vitamin C deficiency. The rule we have followed has been to suspect deficiency in all cases of hemorrhage and musculo-skeletal weakness. All such patients are tested. A number

* Urinary output expressed in mgs. and percentage of intake.

are found who seem to be truly depleted and who benefit from specific treatment.

Finally, a few words concerning treatment. The vitamin may be given in the crystalline form, as tablets, or intravenously. It may be given in food. There are occasions when each method has advantages. The severe scorbutic deserves large doses of the pure substance as well as a model diet. This is true because severe scurvy is a dangerous condition, the depletion is severe and the equivalent of two or three liters of orange juice may be given in a single 10 cc. dose of crystalline vitamin C. Similarly the patient with severe hemorrhage should be given one or two large doses. A large dose is 500 or 1000 mgs. We have used 1000 mgs. as a rule but I believe that 500 mgs. is probably sufficient. Indeed it may be that 100 mgs. will accomplish as much; I do not know. Since the vitamin is nontoxic we have inclined to give large doses. We have never seen a reaction to such dosage. Our practice is to give a gram or a half gram daily.

In the mild scorbutic the vitamin is administered parenterally, if the case suggests faulty absorption or abnormal requirements, and as part of the therapeutic trial, always an illuminating matter. The treatment otherwise is dietary. The prescription of vitamin tablets would seem to have a very limited usefulness.

The use of vitamin C in pills containing all of the known vitamins and as a prolonged substitute for a correct diet appears to be a serious mistake. In the first place the stability of the vitamin in natural sources is infinitely greater than in the pure form. Twenty-five years ago Funk remarked on the stability of vitamin C in lemon juice where it withstands heating to 110 degrees. Buffers present in fruit juices are protective probably within the man as well as outside him. In the second place, the natural sources contain other vitamins, minerals and probably many wholly unrecognized factors of advantage. Thus several careful workers have demonstrated that supposedly pure but extracted vitamin C had attributes not present in the synthetic preparations. We have yet to recognize all of the vitamins if indeed we ever shall be able. The shotgun vitamin pill is therefore not a substitute for a proper diet. It is also unsound because those individuals able to afford such treatment usually do not need it while those who might be benefited are unable to buy it. A dollar will buy more vitamins in the market than in the drug store.

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